GANETESPIB

BACKGROUND INFORMATION FOR THE PEDIATRIC SUBCOMMITTEE MEETING OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

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Synta Pharmaceuticals Corporation
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LIST OF ABBREVIATIONS

Abbreviation or Term	Meaning
17-AAG	17-allylamino-17-demethoxygeldanamycin
AE(s)	adverse event(s)
AKT	a serine/threonine kinase (also known as protein kinase B (PKB)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BRAF	V-RAF murine sarcoma viral oncogene homolog B1
CL	clearance
C_{max}	maximum drug concentration
c-MET	hepatocyte growth factor receptor (cellular)
CNS	central nervous system
c-SRC	proto-oncogenic tyrosine kinase (cellular)
CR	complete response
CT	computed tomography
CYP	cytochrome P450
CYP2C19	cytochrome P450 2C19
CYP3A4	cytochrome P450 3A4
DDI	drug-drug interactions
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eIF2α	Eukaryotic translational initiation factor 2 alpha
ER	Endoplasmic reticulum
ERK	extracellular signal-regulated kinase
FLT3	FMS-like tyrosine kinase 3
G6PD	Glucose 6-phosphate dehydrogenase
GCP	Good Clinical Practice
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
GLP	Good Laboratory Practice

Abbreviation or Term	Meaning
h	hour(s)
HCC	Hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HNSTD	highest non-severely toxic dose
HSP70	heat shock protein 70
Hsp90	heat shock protein 90 (human)
IC_{50}	drug concentration that inhibits cell growth by 50%
IST	Investigator-sponsored (clinical) trial
JAK	Janus kinase
kg	kilogram
K-Ras	Kirsten rat sarcoma viral oncogene homolog
L	litre
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	millilitre
MPNST	Malignant peripheral nerve sheath tumor
ms	milliseconds
MTD	maximum tolerated dose
µM	micromolar
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nM	nanomolar
NOAEL	no observable adverse effect level
NOEL	no observable-effect level
NSCLC	non-small cell lung carcinoma(s) (or cancer[s])
ORR	objective response rate
OS	overall survival
PD	progressive disease
PEG	polyethylene glycol
PFS	progression-free survival
P-gp	P-glycoprotein
POC	proof of concept
PR	PR interval of an ECG (unless noted to be: Partial response)
QT	QT interval of an ECG

Abbreviation or Term	Meaning
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
SAE(s)	serious adverse event(s)
SCLC	small cell lung carcinoma (or cancer)
SD	standard deviation (unless noted to be: Stable disease)
SEM	standard error of the mean
SOC	System Organ Class
ganetespib (STA-9090)	5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-2,4-dihydro-4-(1-methyl-1*H*-indol-5-yl)-3*H*-1,2,4-triazole-3-one
STAT	signal transducer and activator of transcription
$t_{1/2}$	terminal half life
TKI	tyrosine kinase inhibitor
TTF	time-to-treatment failure
UDP	uridine diphosphate
UGT	UDP-glucuronosyltransferase
USP	United States Pharmacopeia
VEGFR	vascular endothelial growth factor receptor
V_{ss}	volume of distribution at steady state

1. INTRODUCTION

Heat shock protein 90 (Hsp90) is one of the most highly conserved and abundant proteins in mammalian cells, where it serves as a molecular chaperone to maintain the stabilization of intracellular and extracellular proteins. Hundreds of Hsp90 clients have been identified to date, many of which play critical roles in signal transduction, cell cycle control and DNA repair including: mutant p53, AKT, ATR, mutant BRAF, BRCA1, CDK1/4, CHK1, EGFR, EML4-ALK, HER2, HIF1-α, IGF-1R, MET, VEGFR, and steroid receptors[1,2]. It has recently been shown that >60% of human kinases are clients of Hsp90[3].

Hsp90 is overexpressed in a range of cancers, and may contribute to tumor cell survival and metastasis by stabilizing aberrant signaling proteins, interfering with apoptosis and promoting migration and invasion[4-6]. Thus, one unique characteristic of targeting Hsp90 in cancer is that inhibition results in the simultaneous degradation of hundreds of client proteins and combinatorial blockade of multiple signal transduction cascades, thereby potentially bypassing pathway redundancies often found in cancer cells[7-12]. This strategy is quite distinct from other targeted inhibitors (ie, kinase inhibitors), which typically are designed to block a single oncoprotein/pathway.

Another unique feature of Hsp90 inhibitors is their tumor selectivity. Small molecule inhibitors of Hsp90, including Synta's drug candidate ganetespib, are retained in tumors for as much as 20 times longer than in blood or normal tissue[11]. Recently published work suggests that cellular transformation is accompanied by a post-translational modification of Hsp90 (SUMOylation) which enhances the recognition of Hsp90 by ATP competitive inhibitors, thus providing an explanation for the sensitivity of cancer cells to Hsp90 inhibitors relative to normal cells[13].

Ganetespib (formerly called STA-9090) is a novel, injectable resorcinolic triazolone small molecule inhibitor of Hsp90. Ganetespib inhibits the growth of many tumor types in vitro and in vivo including AML, ALL, CML, NHL, neuroblastoma, Ewing sarcoma, rhabdoid cancer, rhabdomyosarcoma, melanoma, and carcinomas of the breast, lung, prostate, bladder and colon[7-10,14-27]. Ganetespib is currently being studied in multiple adult oncology indications. A Phase 3 study of ganetespib in combination with docetaxel in patients with advanced non-small cell adenocarcinoma of the lung is currently in progress. In a potential pediatric indication, a Phase 1 combination study of ganetespib with sirolimus is currently ongoing to assess the safety, tolerability, and maximum tolerated/recommended dose of the combination in patients ≥ 18 years of age with refractory sarcomas or unresectable or metastatic sporadic or neurofibromatosis type-1 associated Malignant Peripheral Nerve Sheath Tumors (MPNST). A Phase 2 study is planned to evaluate the potential clinical benefit of ganetespib in combination with sirolimus for patients with unresectable or metastatic sporadic or neurofibromatosis type-1 associated MPNST; this study will include patients ≥16 years of age.

2. REGULATORY HISTORY

The initial IND for ganetespib was opened in September, 2007. An End-of-Phase 2 meeting to discuss the non-small cell lung cancer indication was held in October, 2012. An initial Pediatric Study Plan requesting a waiver for the lung cancer indication was submitted in March 2013 fulfilling Synta's requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of NDA/BLA submission. In the EU, the EMA Pediatric Committee agreed that the lung cancer indication was eligible for a class waiver for pediatric studies.

3. PRECLINICAL DATA SUPPORTING CLINICAL STUDIES

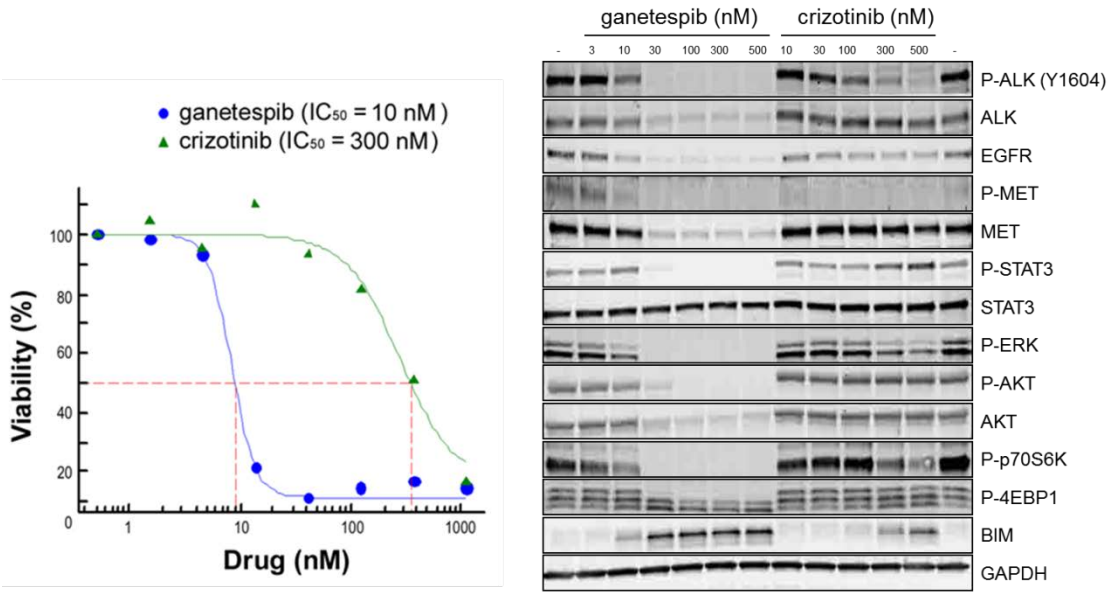
3.1. Pharmacology

3.1.1. Ganetespib Disrupts Multiple Pathways Involved in Tumorigenesis

Hsp90 is a ubiquitously expressed molecular chaperone that functions to maintain the active state of hundreds of conformationally labile signaling proteins, many of which play crucial roles in *establishing* cancer cell hallmarks including cancer initiation, evasion of cell death, limitless replication, sustained angiogenesis, and invasion/metastasis. Inhibiting the intrinsic ATPase activity of Hsp90 with small molecule drugs results in the near simultaneous destabilization and degradation/aggregation of these 'client' proteins and deactivation of their downstream effectors[17]. Ganetespib is a highly potent second generation synthetic inhibitor of Hsp90 which was shown to disrupt the interaction of Hsp90 with more than half of the ~500 known human kinases [3].

To demonstrate the activity of ganetespib on cancer initiation and apoptosis, EML4-ALK dependent H3122 NSCLC cells were treated with ganetespib for 24 hours. Figure 1 shows that treatment with 30 nM ganetespib promotes the degradation of the oncogenic driving kinase, EML4-ALK, and subsequent deactivation of its downstream signaling effectors p-AKT and p-ERK resulting in cell death[10]. In addition, the kinases AKT, EGFR, and MET were degraded resulting in the dephosphorylation of STAT3 and 4EBP1. Selective inhibition of ALK kinase activity by crizotinib also kills H3122 cells but at a concentration 30-100 times that of ganetespib.

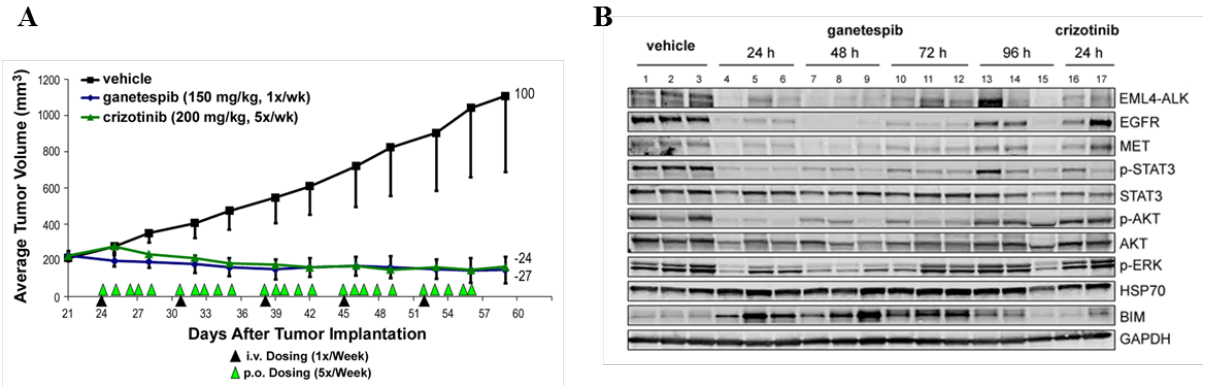
Figure 1: Ganetespib Inhibits ALK+ NSCLC Cell Proliferation Via ALK Degradation



H3122 NSCLC cells were treated with ganetespib or the ALK inhibitor, crizotinib, for 72 hours; viability was assessed via cellular ATP levels (left). H3122 NSCLC cells were treated with ganetespib or crizotinib, as indicated, for 24 hours; lysates were analyzed by Western blot (right).

Similar effects were observed in vivo, where animals bearing H3122 tumor xenografts treated with ganetespib once weekly at the maximum tolerated dose (MTD) showed significant and durable tumor regression comparable to crizotinib (Figure 2). To determine whether tumor response correlated with target modulation, pharmacodynamic (PD) analysis was performed on separate animals treated with one dose of ganetespib or crizotinib. EML4-ALK and downstream ERK signaling were degraded and deactivated, respectively, within 24 hours following ganetespib treatment. These effects were sustained over time, as recovery did not occur until 72-96 hours later. Similar kinetics were observed for other kinase clients (EGFR, MET), and their effector signaling intermediates p-STAT3 and p-AKT. Loss of these signaling cascades was associated with a corresponding increase in BIM protein expression, indicative of apoptosis.

Figure 2: Ganetespib Induces Regression of ALK+ NSCLC Xenografts



(A) Nude mice bearing H3122 xenografts were dosed with ganetespib (1x/wk) or crizotinib (5x/wk) as indicated for 5 weeks. Error bars are the SEM.
(B) PD analysis of client protein modulation in animals bearing H3122 xenografts treated with a single dose of vehicle, ganetespib (50 mg/kg) or crizotinib (50 mg/kg). Tumors were harvested at indicated timepoints post-dose.

Ganetespib has demonstrated antitumor activity in several other human xenograft tumor models driven by an Hsp90 client protein, including leukemia models driven by mutant JAK2 or FLT3[9], NSCLC models driven by EGFR or HER2[28], breast cancer models dependent on HER2[7], melanoma models driven by mutant BRAF[16], and prostate cancer models dependent on the androgen receptor[8]. Thus, targeting the Hsp90 chaperone with ganetespib represents a potentially effective strategy for therapeutic intervention in client protein-driven malignancies, or as a mechanism to reduce multiple cancer signaling networks.

3.1.2. Ganetespib Reduces Tumor Angiogenesis, Invasion, and Metastasis

In addition to its role in tumor initiation and survival, Hsp90 supports multiple facets of the metastatic process[29-31]. In vitro, ganetespib was previously shown to:

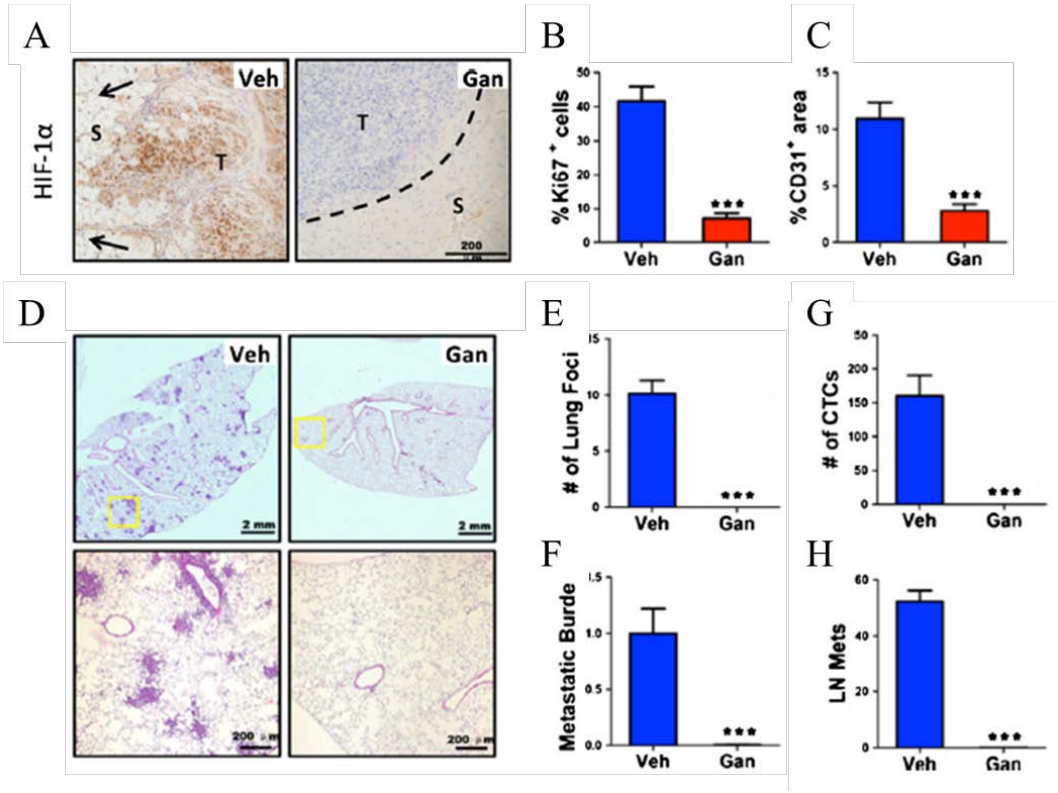
1. Block the directional migration of MDA-MB-231 triple negative breast cancer (TNBC) cells,
2. Significantly reduce TNBC cell invasion,
3. Kill patient derived breast cancer stem cells[32], and
4. Induce the degradation of proteins involved in invasion and metastasis including FAK, MET, and HIF-1α[23,25,31].

HIF-1α plays an important role in tumor metastasis by controlling the expression of multiple angiogenic and migratory factors including MMPs, MET, P4HA1, and VEGF[33]. Inhibition of HIF-1α activity dramatically inhibits tumor vascularization in animal models, and the transcription factor is a known client protein of Hsp90[34,35].

In vivo, ganetespib treatment negatively impacts tumor invasion and metastasis in orthotopic metastasis models of TNBC (Proia et al., 2014; Xiang et al., 2014). Shown in Figure 3D, vehicle treated animals develop substantial lung metastases 44 days after MDA-MB-231

human TNBC cell implantation into the mouse mammary fat pad. Ganetespib reduced the invasion of cancer cells into the surrounding stroma (Figure 3A), metastasis via blood vessels to the lungs (Figure 4D-F), metastasis via lymphatics to the axillary lymph nodes (Figure 3H), and the number of circulating tumor cells (Figure 3G). These effects can be explained in part by reduced HIF-1α expression in the primary tumor (Figure 3A) coordinate with decreased mRNA levels of HIF target genes required for angiogenesis, invasion, and metastasis and consequently decreased tumor vascularization (Figure 3C[31]). Compelling anecdotal evidence of metastatic tumor responses in TNBC patients undergoing ganetespib therapy has also been obtained in the clinical setting (Proia et al., 2014).

Figure 3: Ganetespib Impedes Tumor Angiogenesis, Invasion, and Metastasis



(A) MDA-MB-231 cells were implanted into the mammary fat pad and dosed weekly, 7 days later, with vehicle (Veh) or ganetespib (Gan; 150 mg/kg/wk). IHC from invasive front of primary tumors (T) for HIF-1α ; stroma (S).
*(B) Analysis of cell proliferation by Ki67 and (C) angiogenesis in primary tumor by CD31 staining. ***p <0.001.*
(D) Lungs collected on day 44 from tumor-bearing mice treated with vehicle and ganetespib, stained with (H&E).
(E) Number of metastatic foci per lung section was determined.
(F) Metastatic burden was determined by qPCR of lung genomic DNA with primers for human HK2.
(G) CTCs in peripheral blood were measured by RT-qPCR of total cellular RNA with human 18S rRNA primers.
(H) The axillary lymph node was analyzed by IHC for human vimentin; 6 random fields quantitated.

3.1.3. Ganetespib Activity in Sarcoma Models

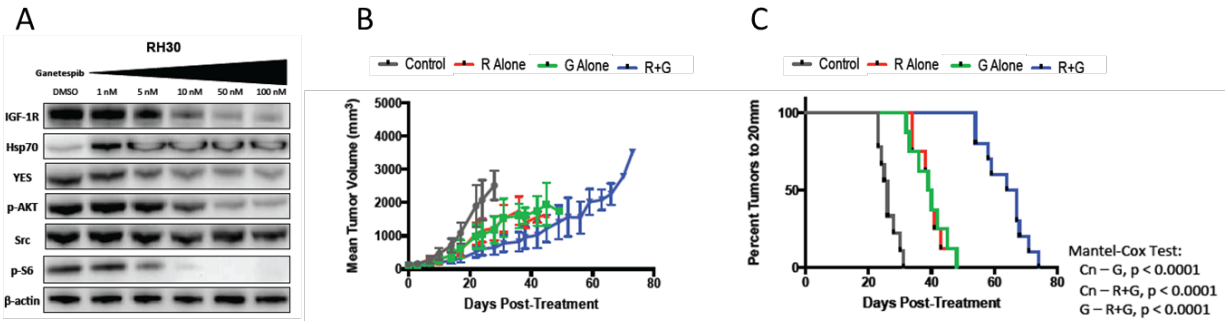
Hsp90 inhibitors have demonstrated activity in a variety of preclinical bone and soft tissue sarcoma models, including synovial sarcoma[36,37], Ewing Sarcoma[38], osteosarcoma[39,40], and rhabdomyosarcoma[41,42]. In Stage 1 preclinical studies performed by the Pediatric Preclinical Testing Program against selected childhood solid tumor and leukemia models, ganetespib demonstrated potent cytotoxic activity with an average IC50 value of 9 nM (Table 1)[27].

Table 1: Comparison of Median IC50 for Cell Line Panels

	RMS	Non RMS	Ewing	Non Ewing	Neuro	Non Neuro	ALL	Non ALL	All Lines
Median rIC_{50} (nM)	7.1	10.1	5.1	10.5	19.6	7.7	11.2	7.7	8.8
P-value	0.33		0.01		0.04		0.92		

While highly potent as a single agent in preclinical models, it is appreciated that cancer represents a heterogeneous cellular population with the ability to quickly develop resistance to single agent therapies. Thus, we have focused on identifying rational combination strategies for a given indication based on common genetic alterations. For example, increased expression of several elements in the PI3K/ATK/mTOR pathway has been identified in many sarcoma subtypes[43]. Further, mTOR has been shown to play a role in the heat shock response elicited by Hsp90 inhibitors that may consequently reduce the therapeutic activity of Hsp90 inhibition[14]. Combining ganetespib with mTOR inhibitors has been shown to synergistically increase antitumor activity in several solid tumor models[14].

Shown below, treatment of rhabdomyosarcoma cells with ganetespib results in the simultaneous degradation and/or deactivation of several factors contributing to AKT signaling including IGF-1R, the Src kinase YES, pAKT, and pS6. In animals bearing rhabdomyosarcoma xenografts tumors, ganetespib and the mTOR inhibitor rapamycin display comparable single agent activity but when combined show a significant improvement in survival.



Enhanced mTOR signaling is commonly observed in malignant peripheral nerve sheath tumors (MPNSTs), and components in the mTOR signaling axis (p-mTOR, p-S6RP) are independent poor prognostic factors for MPNST[44]. Recent preclinical data has shown that MPSNTs are highly aneuploid and have high levels of ER stress compared to normal peripheral nerves. Hsp90 inhibitors, which enhance proteotoxic stress, combined with rapamycin have shown synergistic effects in vitro by promoting irresolvable ER stress,

resulting in catastrophic ER and mitochondrial damage. In the Nf1/p53 transgenic mouse tumor model, Hsp90 inhibition with ganetespib was not sufficient to promote tumor regression, but when combined with rapamycin, tumors shrank on average 49%. Tumor regression was visually apparent and histologic analysis revealed massive cell death and accumulating debris. Maximal tumor regression occurred within 3-5 days and no acute or long-term toxicity was observed. To date, no targeted agents have been shown to cause tumor regression in the Nf1/p53 tumor model or in human tumors.

3.2. Nonclinical Pharmacokinetics and Metabolism

Ganetespib exposure (peak plasma concentration and total systemic exposure) increased in an approximately dose-proportional manner in mice, rats, and monkeys over the dose ranges tested. Ganetespib was highly cleared in mice and rats, while CL was moderate in monkeys. Mean terminal half-life ($t_{1/2}$) values for ganetespib in the multiple dose studies were approximately 6 and 11 hours in rats and monkeys, respectively. No marked sex differences were observed in the PK of ganetespib in either rats or monkeys.

Ganetespib was highly protein-bound and highly distributed throughout nearly all tissues; however, there was limited distribution into the central nervous system (CNS). Ganetespib was extensively metabolized in liver to mainly glucuronide conjugates. Ganetespib is excreted through feces; this is the major route of excretion. Ganetespib does not appear to accumulate after multiple dosing. Two glucuronide conjugates did not show in vitro activity in a HER2 degradation assay.

Ganetespib is metabolized primarily to glucuronide conjugates mediated by UGT1A9 and, to a lesser extent, by UGT1A1, UGT1A3, UGT1A7, UGT1A8, and UGT1A10. Ganetespib is a substrate for P-gp but not BCRP or hepatic uptake transporters (OCT1, OATP1B1, and OATP1B3). Ganetespib inhibits activities of CYP2C19 and CYP3A4 (midazolam specific) in human liver microsomal systems but does not markedly inhibit transporters including P-gp. Ganetespib does not appear to be an inducer of CYP or UGT enzymes. Ganetespib inhibited UGT-mediated metabolism of potential co-medications to some extent in human hepatocytes.

3.3. Safety Pharmacology

Ganetespib was evaluated for general/safety pharmacology effects in a panel of receptor-binding assays in vitro and in a rabbit Langendorff heart preparation ex vivo. Both studies were non-Good Laboratory Practice (GLP). In addition, a GLP rising-dose cardiovascular assessment was conducted in cynomolgus monkeys.

In the receptor-binding study, 67 targets were evaluated. The glucocorticoid receptor was the most sensitive to inhibition with ganetespib, with an IC_{50} of 0.243 micromolar (µM). The C_{max} at 1 mg/kg in the cynomolgus monkey (HNSTD), when corrected for plasma protein binding, was less than 10 nM, which is at least 20 times lower than the IC_{50} value for inhibition of glucocorticoid receptor.

In the Langendorff study, rabbit hearts were perfused with vehicle (dimethylsulfoxide [DMSO] in Krebs solution) followed by escalating concentrations of ganetespib (10^{-8}, 10^{-7},

10^{-6}, 10^{-5}, and 10^{-4} M) for 15 minutes each. Ganetespib minimally decreased the rate of atrioventricular (AV) conductance at 10^{-6} M and 10^{-5} M. At 10^{-4} M, the PQ interval was not measurable because of arrhythmia. Also at 10^{-4} M, the QRS duration increased, a second degree AV block was produced, and occasional supraventricular premature depolarization occurred. Other cardiac parameters were not significantly altered by ganetespib. Results with the positive control, quinidine, confirmed that the test system was sensitive to treatment-induced effects. The C_{max} at 1 mg/kg in the cynomolgus monkey (HNSTD), when corrected for plasma protein binding, was less than 10^{-8} M, which is at least 100 times lower than the minimum concentration (10^{-6} M) that caused the PQ interval increase.

In the rising-dose cardiovascular assessment, cynomolgus monkeys were administered 0 (vehicle) or 7, 9, or 11 mg/kg of ganetespib by 1-hour IV infusion. There were no ganetespib-related changes in the mean arterial blood pressures or heart rates and no qualitative or quantitative ganetespib-related electrocardiogram (ECG) changes. There was a dose-independent reduction in body temperature beginning ~8 hours post dosing (the start of the next dark cycle). Body temperature was normal ~24 hours post dosing.

3.4. Toxicology

Rats survived a single 30 mg/kg dose of ganetespib, but doses of 85 or 250 mg/kg elicited moribundity and mortality. Rats given 10 or 30 mg/kg twice weekly for 4 weeks survived and were in good clinical condition. In contrast, rats given 100 mg/kg (reduced to 85 mg/kg beginning with the third dose) had pronounced clinical signs of systemic toxicity such as emaciation and decreased activity. Several of these animals died or were euthanized early. For 100/85 mg/kg rats assigned to a 14-day recovery evaluation, most changes returned to normal or improved. Male rats given 10, 30, 75, or 100 mg/kg once weekly for 4 weeks had no abnormal clinical findings; dose-related gross and microscopic changes occurred at 30, 75, and 100 mg/kg.

The maximum tolerated single-administration dose in cynomolgus monkeys was 11 mg/kg. When administered on 2 consecutive days, up to 3 mg/kg/day was well tolerated. Cynomolgus monkeys tolerated a 1 mg/kg dose of ganetespib, administered twice weekly for 4 weeks. A monkey given 3 mg/kg was euthanized moribund; the dose was reduced to 1 mg/kg and remaining monkeys given the reduced dose were clinically normal. Monkeys given 6 mg/kg (reduced to 4 mg/kg) or 11 mg/kg (reduced to 9 mg/kg) exhibited clinical signs consistent with GI tract changes observed pathologically. Two monkeys given 11/9 mg/kg were euthanized moribund. The incidence of histopathologic findings (in stomach and/or large intestine, adrenal gland, pancreas, and thymus) was lower in 11/9 mg/kg and 6/4 mg/kg monkeys assigned to a 2- to 4.5-week recovery evaluation.

In 3-month studies, ganetespib was administered on Days 1 and 15 of four 21-day cycles. Rats receiving that regimen tolerated 20 mg/kg/dose of ganetespib, the NOAEL. Transient decreases in weight gain occurred at 50 and 100 mg/kg/dose, and early deaths occurred at 100 mg/kg/dose. Cynomolgus monkeys in that regimen tolerated doses up to 7 mg/kg/dose, the NOAEL. Transient diarrhea occurred at 2, 4, and 7 mg/kg/dose, with reversible microscopic pathologic changes occurring at 7 mg/kg/dose.

Ganetespib was considered to be well tolerated by cynomolgus monkeys when administered by 1-hour infusion twice weekly for 4 weeks via an implanted silicone venous catheter.

When pregnant female rats were given ganetespib daily by infusion during organogenesis, doses up to 1 mg/kg/day did not elicit effects on maternal or fetal parameters. Maternal toxicity (clinical signs, decreased weight gain and food consumption) and developmental toxicity (postimplantation loss) occurred at doses of 3 mg/kg/day and higher.

Ganetespib was not found to be mutagenic or clastogenic in vitro, but was clastogenic in the in vivo rat micronucleus assay.

As with the negative-control compound, 17-AAG (which has not been associated with ocular toxicity in the clinic), ganetespib was rapidly eliminated from retinal tissue and did not cause photoreceptor cell apoptosis[45]. Unlike 17-DMAG and AUY922, ganetespib was not associated with ocular toxicity in the rat model, suggesting that profiles of retina/plasma exposure and retinal elimination rate play crucial roles in the onset of ocular toxicity. The ratio of the concentration of drug in retina and plasma, as well as the speed with which drug in the retina is cleared from that tissue, differ among the drugs tested, and was predictive of ocular toxicity.

4. CLINICAL TRIAL EXPERIENCE IN ADULTS

4.1. Overview

Ganetespib has been studied in 5 completed Synta-sponsored clinical trials (Studies 9090-02, 9090-03, 9090-04, 9090-05, and 9090-07) and 3 completed Synta-sponsored studies in normal healthy volunteers (9090-12, 9090-13, and 9090-15). Ganetespib is currently being studied in 6 Synta-sponsored clinical trials. Studies include: one Phase 1 study, three Phase 2 studies, one Phase 2b study, and one Phase 3 study. Ganetespib is also being studied in 24 Investigator Sponsored Trials (ISTs), 15 of which are currently enrolling patients. The majority of ISTs are proof-of-concept studies across a variety of tumor types as well as hematologic malignancies. The ISTs currently enrolling include: five Phase 1/2 studies, four Phase 1 studies, four Phase 2 studies, one Phase 2/3 study, and one Phase 3 study.

As of 20 September 2014, 1,258 individuals have received at least 1 dose of ganetespib in one of these 31 studies. A total of 402 patients have been treated with single-agent ganetespib (Studies 9090-01 through Study 9090-06, Study 9090-09, and Study 9090-11). A total of 422 patients have been treated with ganetespib in combination with docetaxel in Studies 9090-07, 9090-08, and 9090-14. In Synta-sponsored studies of normal healthy volunteers, 104 subjects have received ganetespib: 8 in the Human Mass Balance study (9090-12), 48 in the Thorough QT study (9090-13), and 48 in the DDI study (9090-15). The remaining patients (330) have been treated in ISTs.

Two Synta-sponsored Phase 1 studies evaluated the safety, tolerability, and preliminary activity of ganetespib in patients with solid tumors: Study 9090-01 (n=86) and Study 9090-02 (n=53). In these studies, single-agent doses ranged from 7 to 259 mg/m^2, once-weekly

administration, and 2 to 200 mg/m^2, twice-weekly administration, 72-hour interval between doses. In addition, consecutive-day, twice-weekly dosing was also studied with doses of 50, 75, and 100 mg/m^2. Ganetespib was administered 3 consecutive weeks of a 4-week cycle. The recommended Phase 2 doses for single-agent ganetespib in this population are 200 mg/m² once weekly and 150 mg/m² twice weekly (72-hour interval between doses).

Two Synta-sponsored studies have evaluated the safety, tolerability, and preliminary antitumor activity of ganetespib in patients with hematologic malignancies: Study 9090-03 (n=31) and Study 9090-04 (n=29). In these studies, single-agent doses ranged from 14 to 100 mg/m^2 (n=31) twice weekly and 120, 150, and 200 mg/m^2 (n=29) once weekly, respectively. Unlike the solid tumor studies, no rest week was incorporated into the dosing schedule. Patients received ganetespib once or twice weekly for 4 consecutive weeks of a 4 week cycle. The doses selected for further study in this population were 200 mg/m^2 once weekly and 90 mg/m^2 twice weekly.

The Phase 2 program was designed to evaluate the antitumor activity of ganetespib in a variety of solid tumors. This includes 4 single-agent, proof-of-concept studies sponsored by Synta: Study 9090-05 (n=27) in GIST, Study 9090-06 (n=113) in NSCLC, Study 9090-09 (n=12) in ALK-positive NSCLC, and Study 9090-11 (n=27) in breast cancer. In addition, Study 9090-06 was amended to offer ganetespib in combination with weekly docetaxel to a subset of NSCLC patients after treatment with single-agent ganetespib.

The clinical development program was expanded to evaluate ganetespib in combination with docetaxel in patients with solid tumors. In Study 9090-07 (n=27), the recommended combination dose is 150 mg/m^2 ganetespib on Days 1 and 15 and 75 mg/m^2 docetaxel on Day 1 in a 21-day cycle in patients with solid tumors.

Following identification of the recommended combination dose for Phase 2 in Study 9090-07, a Phase 2b/3 Study 9090-08 was initiated in order to evaluate the safety and activity of ganetespib in combination with docetaxel vs. docetaxel alone in second-line advanced NSCLC. A Phase 3 study (9090-14) of ganetespib in combination with docetaxel vs. docetaxel alone in second-line advanced NSCLC patients at least 6 months from date of diagnosis of advanced disease is currently in progress.

Synta-sponsored and Investigator-sponsored clinical trials are summarized in Appendix 1 and 2 respectively. In these studies, ganetespib has been used both as monotherapy and in combination with a variety of anti-tumor treatments including: docetaxel, paclitaxel, bortezomib, cytarabine, capecitabine+radiation, trastuzumab, crizotinib, carbo- and cis-platin, and fulvestrant. For details of dose and schedule please see the Appendices.

4.2. Clinical Pharmacology

4.2.1. Pharmacokinetics

The PK of ganetespib, administered at various doses on a weekly or twice-weekly schedule, are under investigation or have been completed in 11 clinical trials. Preliminary or final data and calculated parameters are available from these trials in patients with solid and

hematologic tumors and normal healthy male subjects, and are summarized below. PK data from patients with hepatic dysfunction from a hepatocellular carcinoma (HCC) IST study are also available.

Ganetespib PK shows distribution and elimination phases with concentrations declining by approximately 10-fold within the first hour and nearly 100-fold within 10 hours following infusion termination. Mean terminal half-lives have ranged from approximately 5 to 15 hours in most studies. In the human mass balance study, where PK sampling was most complete and longest (through 96 hours), the mean plasma terminal half-life was 17.9 h (n=8). In the HCC IST study, consisting of 13 patients with mild hepatic dysfunction (Child-Pugh Class A) and 1 patient with moderate hepatic dysfunction (Child-Pugh Class B), the mean half-life was 6.45 h. Ganetespib plasma concentrations following the first and subsequent doses are comparable following either once or twice-weekly dosing, indicating the lack of drug accumulation. Ganetespib plasma concentrations are also comparable in the solid and hematologic tumor patients. Mild hepatic dysfunction did not alter ganetespib PK. C_{max} and AUC increase in approximate proportion to dose irrespective of dosing day with comparable dose-exposure ratios for doses given on different days, indicating linear PK. At doses of 150 mg/m^2 and 200 mg/m^2, AUC values of approximately 5600 ng·h/mL and 7600 ng·h/mL are generally expected, respectively. At these same doses, C_{max} values of approximately 3500 ng/mL and 5000 ng/mL, respectively, are generally expected. Ganetespib C_{max} correlates well with AUC ($r^2 = 0.9309$). CL and V_d are approximately constant across therapeutic doses. Ganetespib median CL is approximately 27 L/h/m^2.

Two ganetespib glucuronide metabolites (STA-12-0671 and STA-12-0672) were quantified. Metabolite STA-12-0671 mean half-life values ranged from 11.9 to 27 hours. Metabolite STA-12-0672 mean half-life values ranged from 6.32 to 17.9 hours. For both metabolites, T_{max} was typically at the end of the ganetespib infusion and PK parameters were consistent across sampling days (Days 1, 8, and 15).

Ganetespib was extensively metabolized to STA-12-0671, and moderately metabolized to STA-12-0672. Based on the comparison of $AUC_{0-\infty}$, exposure to ganetespib accounted for approximately 14% of the total radioactivity in plasma, with exposure to metabolites STA-12-0671 and STA-12-0672 accounting for approximately 50% and 6% of the total radioactivity, respectively, resulting in the classification of STA-12-0671 as a "major" metabolite according to the Metabolites in Safety Testing (MIST) guidance.

The potential for ganetespib to inhibit CYP2C19 substrates' metabolism was explored in a clinical DDI study with omeprazole. Concomitant administration of ganetespib produced a modest (20%) increase in omeprazole exposure as characterized by AUC.

4.2.2. Thorough QT Study

We have observed a QTcF interval prolongation of 21.5 ± 1.2 ms (mean ± SE) in a Thorough QTc clinical study of ganetespib in healthy volunteers at 200 mg/m^2, which is 33% higher than the recommended ganetespib dose for combination studies. An independent review of the ganetespib clinical safety database did not indicate an increased frequency or severity of

cardiovascular adverse events in patients treated with ganetespib. None of the 1258 patients treated with ganetespib to date had torsades de pointes recorded on ECG.

In the Thorough QT Study, one subject out of 46 showed a QTc>450ms and no subjects experienced a QTc>480ms; the number of outliers with change in QTc>30ms was low, only two subjects out of 46 (versus one subject in the placebo group); and there were no subjects with change in QTc>60ms. We have however developed, agreed upon with the FDA, and implemented an enhanced ECG monitoring plan in ganetespib clinical studies for monitoring patient safety and for further characterization of this ECG change.

4.3. Clinical Safety

4.3.1. Adverse Events in Patients Administered Single-Agent Ganetespib

Table 2 summarizes all treatment-emergent AEs in patients who received at least 1 dose of single-agent ganetespib and for whom AE data were available as of 20 September 2014 (n=402).

Table 2: Integrated Summary of Treatment-Emergent Adverse Events, Single-Agent Ganetespib

	All Patients N=402 (%)
Number of Patients with at Least 1 AE	399 (99.3)
Number of Patients with at Least 1 AE with NCI/CTC Grade of ≥3	274 (68.2)
Number of Patients with at Least 1 Related AE[a]	370 (92.0)
Number of Patients with at Least 1 Related AE[a] with NCI/CTCAE Grade of ≥3	125 (31.1)
Number of Patients with at Least 1 SAE	160 (39.8)
Number of Patients with at Least 1 Related SAE[a]	33 (8.2)
Number of Patients with at Least 1 AE Leading to Study Drug Discontinuation	54 (13.4)
Number of Patients with at Least 1 AE Leading to Death	44 (10.9)

[a] The Related AEs/SAEs are those with a relationship of Possible, Probable, Definite, Unknown, or Missing.
Note: At each patient summarization, a patient is counted once if the patient reported one or more events.

A summary of treatment-emergent and treatment-related AEs occurring in ≥10% of patients treated with single-agent ganetespib is presented in Table 3. Ninety-nine percent (399/402) of patients who received at least 1 dose of ganetespib experienced a treatment-emergent AE. The most frequent treatment-emergent AE was diarrhea, which occurred in 320 (80%) patients, followed by fatigue, nausea, and decreased appetite which occurred in 214 (53%), 177 (44%), and 126 (31%) patients, respectively.

Table 3: Integrated Summary of Most Frequent (≥10%) Treatment-Emergent and Treatment-Related Adverse Events in Single-Agent Studies, by Preferred Term

MedDRA Preferred Term[a]	Most Frequent AEs (N=402) n (%)	Most Frequent Related AEs (N=402) n (%)
Number of Patients with at least One Adverse Event	399 (99.3)	370 (92.0)
Diarrhoea	320 (79.6)	308 (76.6)
Fatigue	214 (53.2)	148 (36.8)
Nausea	177 (44.0)	143 (35.6)
Decreased appetite	126 (31.3)	74 (18.4)
Vomiting	109 (27.1)	77 (19.2)
Constipation	88 (21.9)	14 (3.5)
Anaemia	85 (21.1)	29 (7.2)
Insomnia	85 (21.1)	32 (8.0)
Abdominal pain	81 (20.1)	40 (10.0)
Headache	81 (20.1)	34 (8.5)
Dyspnoea	70 (17.4)	11 (2.7)
Aspartate aminotransferase increased	65 (16.2)	26 (6.5)
Blood alkaline phosphatase increased	65 (16.2)	37 (9.2)
Back pain	63 (15.7)	7 (1.7)
Alanine aminotransferase increased	62 (15.4)	36 (9.0)
Weight decreased	62 (15.4)	27 (6.7)
Dehydration	59 (14.7)	29 (7.2)
Hypokalaemia	55 (13.7)	23 (5.7)
Hyponatraemia	54 (13.4)	14 (3.5)
Dizziness	53 (13.2)	18 (4.5)
Oedema peripheral	53 (13.2)	8 (2.0)
Cough	52 (12.9)	3 (<1)
Asthenia	42 (10.4)	19 (4.7)

[a] A patient counts once for a preferred term with any incidence of the event.

Of the 402 patients who received at least 1 dose of ganetespib in single-agent studies, 274 (68%) patients had a Grade ≥ 3 AE. The most common AEs that were Grade 3 or higher were diarrhea (10%), fatigue (10%), hyponatremia (8%), neoplasm progression (7%), and anemia (5%).

A total of 125 (31%) patients had aGrade ≥ 3 AE that was considered related to treatment. The most common treatment-related AEs Grade ≥ 3 were diarrhea (10%), fatigue (6%), increased lipase (3%), hyponatremia (2%), and hypophosphatemia, nausea, increased ALT, and increased AST (2% each).

Of the 402 patients for whom integrated AE data were available, 160 patients (40%) experienced a treatment-emergent AE that was assessed as serious. The most common SAEs (≥4 patients) were neoplasm (disease) progression, which occurred in 28 patients (7%); followed by pneumonia (13, 3%); febrile neutropenia (9, 2%), dyspnea and vomiting (8 each, 2%); abdominal pain, diarrhea, and nausea (7 each, 2%); dehydration, hyponatremia, pleural effusion, and renal failure acute (5 each, 1%); and anemia, asthenia, cellulitis, fatigue, pain, and pulmonary embolism (4 each, <1%).

Thirty-three (8%) of the patients experienced an SAE assessed as related to treatment. The most common treatment-related SAE was diarrhea, which occurred in 7 (1.7%) patients. All other treatment-related SAEs occurred in <1% of study patients. None of the events of neoplasm progression was assessed as treatment-related. The majority of fatal AEs were due to disease progression. Only one event of cardiac arrest and one event of acute renal failure were considered related to ganetespib treatment.

Table 4: Integrated Summary of Most Frequent (≥1%) Treatment-Emergent and Treatment-Related Serious Adverse Events by Frequency, Single-Agent Ganetespib

MedDRA Preferred Term[a]	SAEs (N=402) n (%)	Related SAEs (N=402) n (%)
Number of Patients with at least One Adverse Event	160 (39.8)	33 (8.2)
Neoplasm progression	28 (7.0)	0
Pneumonia	13 (3.2)	0
Febrile neutropenia	9 (2.2)	1 (<1)
Dyspnoea	8 (2.0)	0
Vomiting	8 (2.0)	4 (<1)
Abdominal pain	7 (1.7)	1 (<1)
Diarrhoea	7 (1.7)	7 (1.7)
Nausea	7 (1.7)	3 (<1)
Dehydration	5 (1.2)	2 (<1)
Hyponatraemia	5 (1.2)	2 (<1)
Pleural effusion	5 (1.2)	0
Renal failure acute	5 (1.2)	1 (<1)

[a] Patients who experienced multiple instances of an AE are counted once per term.
Related AEs are those with a Relationship of Possible, Probable, Definite, Unknown, or Missing.

4.3.2. Adverse Events in Patients Administered Ganetespib in Combination with Docetaxel

In the integrated data from 223 patients treated with ganetespib in combination with docetaxel from the Phase 2a and 2b NSCLC studies, 98% of patients experienced at least 1 AE, 84% at least 1 treatment-related event. The most frequently reported AEs were related to GI toxicity and included diarrhea (49%), nausea (26%), decreased appetite (18%), vomiting (14%), constipation (11%), Non-GI related events that occurred frequently include neutropenia (51%), consistent with known toxicity related to docetaxel treatment, fatigue (32%), and anemia (28%).

Of the 222 patients treated with ganetespib in combination with docetaxel, 62% had treatment-emergent AEs that were Grade 3 or Grade 4. Forty-one percent had at least 1 SAE and 19%, at least 1 treatment-related SAE. The most common Grade 3 or 4 event in patients receiving the combination treatment was neutropenia (20% and 26%, respectively). In patients treated with docetaxel only, 22% of patients experienced a Grade 3 event of neutropenia and 19% experienced a Grade 4 event. Severe neutropenia was balanced in the study arms and it is a known toxicity of docetaxel. Febrile neutropenia was experienced by 11% of those receiving the combination treatment compared to 5% of patients treated with docetaxel only.

4.4. Clinical Efficacy

While ganetespib is being evaluated in several different adult indications, the lead indication is ganetespib combined with docetaxel for the treatment of patients with advanced non-small-cell lung adenocarcinoma who have progressed following 1st line chemotherapy. A Phase 3 study, 9090-14, is currently in progress. Results are available for the Phase 2b study, 9090-08.

In Study 9090-08, Patients with one prior systemic therapy for advanced disease were eligible. Docetaxel (75 mg/m^2 on Day 1) was administered alone or with ganetespib (150 mg/m^2 on Days 1 and 15) every 3 weeks. Co-primary endpoints were progression-free survival (PFS) in patients with elevated lactate dehydrogenase (eLDH) and mutated KRAS (mKRAS). Pre-specified stratification included patients > 6 or ≤ 6 months since diagnosis of advanced disease.

A total of 385 patients were enrolled and 381 were treated. Early in the trial increased hemoptysis and lack of efficacy was observed in non-adenocarcinoma patients (n=71), therefore only patients with adenocarcinoma histology were subsequently enrolled. Neutropenia was the most common grade ≥3 adverse event: 42% in the ganetespib combination arm vs. 40% in docetaxel-alone. There was no improvement in PFS in the eLDH (N=114, HR 0.92, p=0·3446) or mKRAS (N=89, HR 0.93, p=0.3865) subgroups. In the adenocarcinoma population, PFS (HR 0·85, p=0·1117) and overall survival (OS) (HR 0·87, p=0·1502) favored the combination. Exploratory analysis identified the greatest benefit in the adenocarcinoma patient subgroup enrolled >6-month from diagnosis (n=177): PFS (HR 0·75, p=0·0401); OS (HR 0·71, p=0·0233).

In this study, the ganetespib-docetaxel combination had an acceptable safety profile and, while not meeting the co-primary endpoints, substantially improved PFS and OS in the subgroup of patients >6 months from diagnosis of advanced lung adenocarcinoma.

The Phase 3 study, 9090-14, is comparing the combination of ganetespib and docetaxel vs. docetaxel alone in the 2nd-line advanced non-small cell adenocarcinoma patient population, with overall survival as the primary endpoint. Patients are required to have diagnosis of advanced disease > 6 months and have tumors that are negative for both EGFR mutation and ALK translocation prior to study entry. Approximately 850 patients will be enrolled. This study is currently in progress.

4.5. Other Indications Being Studied in Adults

Ganetespib is currently being studied in 24 investigator sponsored studies in addition to the on-going Phase 3 study in advanced NSCLC. Of these, 5 randomized clinical trials currently in progress or starting in early 2015:

- AML LI-1: A Programme of Development for Older Patients with Acute Myeloid Leukaemia and High Risk Myelodysplastic Syndrome
- AML 18: A Trial for Older Patients with Acute Myeloid Leukaemia and High Risk Myelodysplastic Syndrome
- AML 19: Adults with Acute Myeloid Leukaemia or High-Risk Myelodysplastic Syndrome
- GANNET53: A Two-Part, Multicentre, International Phase I and II Trial Assessing the Safety and Efficacy of the Hsp90 Inhibitor Ganetespib in Combination with Paclitaxel Weekly in Women with High-Grade Serous, High-Grade Endometrioid, or Undifferentiated, Platinum-Resistant Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer
- I-SPY 2: Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2

Results from these trials are not yet available.

5. EMA PIP

The Pediatric Committee of the European Medicines Agency considers the non-small cell lung cancer indication to be eligible for a class waiver for pediatric studies.

6. ONGOING CLINICAL TRIAL WITH RELEVANCE TO PEDIATRICS, ADOLESCENTS AND YOUNG ADULTS

A trial, sponsored by the Sarcoma Alliance for Research through Collaboration (SARC) in refractory sarcomas (Phase I) and malignant peripheral nerve sheath tumors (Phase II), is

currently in progress. The Principal and Co-Principal Investigators are Dr. AeRang Kim at Children's National Medical Center and Dr. Brigitte Widemann at the NCI Pediatric Oncology Branch. The study is SARC 023: A Phase I/II Trial of Ganetespib in Combination with the mTOR Inhibitor Sirolimus for Patients with Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumors.

6.1. Malignant Peripheral Nerve Sheath Tumors

MPNSTs are soft tissue sarcomas arising from peripheral nerve or show nerve sheath differentiation and are associated with a high risk of local recurrence and metastasis[46]. MPNSTs account for 10% of all soft tissue sarcomas, and carry the highest risk for sarcoma specific death among all the soft tissue sarcoma histologies[47].

Approximately half of all MPNSTs arise from individuals with NF1[48], mostly from pre-existing plexiform neurofibromas[49]. At present, complete surgical resection is the only known curative treatment of MPNST and the outcome for resectable, recurrent or metastatic MPNST remains very poor.

6.2. Clinical Trial SARC 023

6.2.1. Rationale

With increasing understanding in the molecular pathogenesis of MPNSTs, clinical trials with targeted agents have become available and histology specific trials in this rare malignancy are feasible[50]. Xenograft[51] and transgenic[52] mouse models of MPNST have become available, and preclinical trials in these models may have great utility in the rational clinical development of targeted agents. Mammalian target of rapamycin (mTOR) has been reported to be hyperactivated in *NF1*-defiencient tumors as a consequence of aberrant Ras signaling[53,54]. Using an *Nf1/p53*-mutant MPNST model, the Cichowski laboratory demonstrated that sirolimus, an mTOR inhibitor, suppressed tumor growth[52] in a potent but cytostatic effect. Thus, identifying alternative targets in combination with mTOR inhibition may be beneficial. Proteotoxic or endoplasmic reticulum (ER) stress is induced when unfolded proteins accumulate in the ER[55]. Oncogenic RAS also causes ER stress[56], and when ER stress levels become insurmountable, cell death ensues, suggesting agents that enhance ER stress may be developed as anti-cancer agents. The Cichowski laboratory demonstrated that further enhancing ER stress using HSP90 inhibitors coupled with sirolimus led to dramatic tumor shrinkage in the transgenic mouse model, which correlated with profound damage to the ER and cell death[57]. Similar tumor regression from this combination extended to a *KRAS* mutant mouse model of NSCLC.

Previously, no targeted agents have been shown capable of causing tumor regression in the highly aggressive genetically engineered MPNST model or in human tumors. Ganetespib is a potent, next generation Hsp90 inhibitor that has shown superior activity to first generation agents in preclinical studies. It has a favorable safety profile and promising anti-tumor activity over a broad range of tumor types in early clinical trials. Sirolimus is commercially

available, oral, and relatively inexpensive. It has a long safety record, demonstrated efficacy in preclinical cancer models, and was used in the transgenic MPNST mouse model.

The clinical translation of this data led to the development of a multi-institutional open label phase I/II trial of ganetespib in combination with sirolimus in patients with refractory MPNST. As there is preclinical data to support this combination may benefit other sarcomas such as Ewings and rhabdomyosarcoma[58], in addition to MPNST, the phase I portion of this trial includes other refractory or relapsed sarcomas. The results of this trial will provide valuable toxicity, tolerability, and pharmacokinetic information for a drug combination with potential uses other Ras driven tumors. By taking agents selected through this model to a clinical trial, we will be able to explore the utility of the mouse model for predicting response in NF1 clinical trials. Importantly, if the combination proves as effective as hypothesized in MPNSTs, it could provide a therapeutic strategy for this highly refractory and aggressive malignancy.

6.2.2. Study Objectives

Primary Objective

1. Phase I: To assess the safety, tolerability, and maximum tolerated/ recommended dose of ganetespib when administered in combination with sirolimus in patients with refractory sarcomas including unresectable or metastatic sporadic or neurofibromatosis type 1 (NF1) associated MPNST.
2. Phase II: To determine the clinical benefit of ganetespib in combination with sirolimus for patients with unresectable or metastatic sporadic or neurofibromatosis type 1 (NF1) associated MPNST.

Secondary Objectives

1. Phase I: To describe the plasma pharmacokinetic profile of ganetespib and sirolimus when administered in combination therapy
2. Phase I/II: To determine changes in pharmacodynamic parameters including phospho-S6, phosphorylated eIF2 alpha, Akt Phosphorylation, Hsp70, and G6PD in tumor tissue and peripheral blood mononuclear cells at baseline and during treatment and correlate with changes in clinical or radiologic outcome.
3. Phase I/II: To assess patient-reported pain severity and the impact of pain on daily activities before and during treatment with ganetespib and sirolimus and to correlate with changes in clinical or radiologic outcome.
4. Phase I/II: To evaluate the utility of three-dimensional MRI (3D-MRI) analysis in comparison to 1-dimensional and 2-dimensional measurements as a method to more sensitively monitor response.

6.2.3. Trial Design

The study is a multi-institutional open label phase I/II trial of ganetespib in combination with sirolimus in patients with refractory sarcoma including MPNST. The primary objective of the initial component is to determine the safety, tolerability and recommended dose of this novel combination in a limited dose escalation phase I trial. Hsp90 inhibitors and mTOR inhibitors have also both demonstrated benefit in a variety of preclinical bone and soft tissue sarcoma models. We hypothesize that these agents that work on separate and potentially synergistic pathways will also be beneficial for other refractory bone and soft tissue sarcomas. Thus, the phase I component will be open to patients with refractory sarcomas, which will also expedite enrollment. Ganetespib will be given intravenously over one hour on days 1, 8, and 15 every 28 days. Sirolimus will be given orally daily continuously (28 days = 1 cycle). Upon determination of the recommended dosing, the primary objectives of the phase 2 portion will be to determine the clinical benefit rate (CR, PR, or stable disease ≥ 4 months using WHO criteria) of ganetespib in combination with sirolimus for patients with refractory MPNST. Secondary objectives include determination of the pharmacokinetic profile of these agents in combination and pharmacodynamic markers in tumor tissue and peripheral blood mononuclear cells, patient reported pain outcomes, and volumetric MRI analysis of tumor measurement.

Maximum Total Number of Subjects

Phase I: 3 to 6 patients per cohort with 1 dose escalations (potential for 2 de-escalations). Thus a minimum of 6 patients to a maximum of 18 patients are required.

Phase II: 10 patients in first stage with an additional 10 patients in the second stage for a total of 20 patients. The maximum number of evaluable patients for entire study will be 38.

Target Population

Individuals ≥ 18 years of age (amendment pending to reduce age at entry to ≥ 16 year of age) with unresectable or metastatic histologically confirmed sporadic or NF1 associated high grade MPNST who have experienced progression after one or more prior regimens of cytotoxic chemotherapy. The phase I component will also be open to patients with other refractory or relapsed sarcomas.

Anticipated Length of Study

Patients will be able to remain on treatment for a maximum of 1 year (13 cycles) as long as they do not experience progressive disease or unacceptable toxicity. It is expected that 15-25 patients will be enrolled per year, and enrollment is expected to be completed in approximately 2.5 years

Study Drug (s)

- Ganetespib intravenous
- Sirolimus 2 mg oral tablets

Dosing and Administration

- Ganetespib will be administered intravenously over 1 hour on days 1, 8, 15 every 28 days
- Sirolimus will be administered once daily continuously
- 1 cycle = 28 days

Efficacy Evaluations

Response evaluations (WHO) with appropriate imaging studies (MRI/CT) will be performed at baseline and prior to odd cycles (3, 5, 7, etc.).

Safety Evaluations/Concerns

History and physical examinations and laboratory evaluations will be routinely performed during treatment study. For the phase I component: The recommended doses will be based on toxicities observed over the first treatment cycle. Dose modifications and management plans are specified in the protocol.

Correlative Studies

- Pharmacokinetic samples will be collected in all phase I patients (mandatory) and in upwards of 10 patients in the phase II component for data and experience at the recommended dose. Detailed pharmacokinetic sampling will occur at steady state during cycle 1.
- Correlative studies evaluating pharmacodynamic parameters on Hsp inhibition (Hsp70), mTOR inhibition (phospho-S6 and Akt Phosphorylation), UPR activation (EIF2α phosphorylation), and oxidative stress (G6PD) will be explored in tumor tissue and peripheral blood mononuclear cells at baseline and during treatment.
- The patient-reported pain evaluation will consist of two validated scales. The Numerical Rating Scale-11 (NRS-11) will be used to assess pain severity, and the Pain Interference Scale from the Brief Pain Inventory will be used to assess the impact of pain on daily activities. These tests will be given prior to treatment and then prior to cycle 3, 5, 9, and 13 when disease evaluation is performed.

Brief Statistical Design

In the phase I component, a conventional 3+3 dose-escalation design is used. The initial starting dose of ganetespib is 150 mg/m^2, approximately 1 dose level below the recommended phase II weekly dose, in combination with the recommended adult dose of sirolimus of 4 mg once daily. This will be followed by one dose escalation of the ganetespib to 200 mg/m^2 weekly (recommended phase II dose) and sirolimus recommended adult dose. The Maximum tolerated dose (MTD)/Recommended dose will be defined as the dose level immediately below the level at which $\geq$ 33% of patients in a cohort experience a dose-limiting toxicity (DLT) based on toxicities observed in the first treatment cycle.

In the phase II component, the primary endpoint will be clinical benefit rate, which will be defined as a CR, PR, or stable disease ≥ 4 cycles. An evaluable patient will be classified as a responder (success) for the primary endpoint if the patient achieves a PR, CR or stable disease at ≥ 4 months. The target clinical benefit rate will be 25%, and a clinical benefit rate ≤ 5% will be considered uninteresting. Using a Simon's optimal two-stage phase II design, the first stage will require 10 patients, with no further accrual if 0 of 10 respond. If ≥ 1/10 patients respond, accrual will continue until a total of 20 patients have been enrolled. If ≥ 3/20 patients respond, this combination will be considered of sufficient activity. Assuming the number of successes is binomially distributed, this design has a one sided alpha of 0.07 and a power of 88% for detecting a true success probability of at least 25% versus the null hypothesis success rate of 5% or less.

7. POTENTIAL CHALLENGES FOR CLINICAL DEVELOPMENT OF GANETESPIB IN PEDIATRIC INDICATIONS

Ganetespib is metabolized principally by the enzyme UGT1A9 and to a lesser extent by other UGT1A subtypes. Strassburg, et. al. reported that UGT1A9 mRNA increased in an age dependent fashion with significantly lower transcript levels in the age groups 6–12 months and 13–18 months compared to adults. No significant difference in transcript level was found between the 19-24 months age group and adults.[59]

The excipients in the ganetespib formulation, PEG-300, polysorbate 80 and alcohol have been used in pediatric formulations. However, the use of polysorbate 80 in neonates and infants may be problematic.

The use of ganetespib in pediatric patients should be evaluated on a case-by-case basis taking into account the potential risks and benefits to the patient.

While ganetespib is highly potent as a single agent in preclinical models, it is appreciated that cancer represents a heterogeneous cellular population with the ability to quickly develop resistance to single-agent therapies. Identifying rational combination strategies for a given indication based on common genetic alterations in pediatric cancers may be challenging.

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APPENDIX 1. SYNTA SPONSORED STUDIES

Table 5: Synta Sponsored Clinical Trials

Protocol Number /Phase	Study Description	Dose Levels		Dosing Schedule
		Level	**Ganetespib**	
9090-01 *Phase 1*	Open-label dose escalation in solid tumors to determine the MTD and PK of twice-weekly ganetespib	1 to 13	2 mg/m^2 to 200 mg/m^2 Consecutive day dosing: 50-100 mg/m^2	Twice weekly 72 hrs between dosing 3 wks+1 wk rest Consecutive day dosing: Twice weekly. 24 hrs between dosing
9090-02 *Phase1*	Open-label dose escalation in solid tumors to determine the MTD and PKs of once-weekly ganetespib	1 to 13	7 mg/m^2 to 259 mg/m^2	Once weekly 3 wks+1 wk rest
9090-03 *Phase 1*	Open-label dose escalation in hematologic malignancies to determine the MTD and PK of twice-weekly ganetespib	1 to 6	14 mg/m^2 to 110 mg/m^2	Twice weekly 4 wks
9090-04 *Phase 1/2*	Open-label dose escalation (Part 1) in hematologic malignancies (AML, ALL, CML) to be followed by an evaluation at MTD	1 to 3	120, 150, or 200 mg/m^2	Once weekly 4 wks
9090-05 *Phase 2*	Open-label in metastatic or unresectable GIST		200 mg/m^2	Once weekly 3 wks+1 wk rest

Protocol Number /Phase	Study Description	Dose Levels		Dosing Schedule
		Level	**Ganetespib**	
9090-06 *Phase 2*	Open-label in Stage IIIB or IV NSCLC with once weekly ganetespib. ganetespib + docetaxel option in subset of patients post treatment single-agent ganetespib		200 mg/m^2 Rollover Cohort[a] 200 mg/m^2 + 30 mg /m^2 docetaxel 200 mg/m^2 + 35 mg /m^2 docetaxel	Once weekly 3 wks+1 wk rest
9090-07 *Phase 1*	Open-label dose-escalation in solid tumors to determine the PKs of once-weekly dosing with ganetespib plus docetaxel		150 mg/m^2 + 60 mg/ m^2 OR 75 mg/m^2 docetaxel 200 mg/m^2 + 75 mg/ m^2 docetaxel 150 mg/m^2 + 75 mg/ m^2 docetaxel	Day 1- combo tx Day 15- ganetespib 2 wks+1 wk rest Day 1, 4, 15
9090-08 *Phase 2B/3*	Randomized, open-label study in Stage IIIb or IV NSCLC		Arm A (control): docetaxel 75 mg/m^2 Arm B (experimental): ganetespib 150 mg/m^2 + docetaxel 75 mg/m^2.	75 mg/m^2 Day 1, 3 wk cycle Ganetespib Days 1 and 15, each 3-wk cycle Docetaxel Day 1 of each 3-wk cycle
9090-09 *Phase 2*	Open label. single arm multicenter study in pts with ALK-positive NSCLC		ganetespib 200 mg/m^2	Once weekly 3 wks+1 wk rest
9090-11 *Phase 2*	An Open-Label Multicenter Phase 2 Window of Opportunity Study Evaluating Ganetespib in Women with Breast Cancer		ganetespib 150 mg/m^2	150 mg/m^2 twice weekly (Days 1, 4, 8, 11, 15, 18) for 3 wks, 1 wk rest

Protocol Number /Phase	Study Description	Dose Levels		Dosing Schedule
		Level	**Ganetespib**	
9090-12 *Phase 1*	Human mass balance study in healthy male volunteers		86 mg/m^2 ganetespib (including ~100 µCi (3.7 MBq) ^{14}C-radiolabled ganetespib)	86 mg/m^2 ganetespib (including ~100 µCi (3.7 MBq) ^{14}C-radiolabled ganetespib)
9090-13 *Phase 1*	Thorough QT/ECG study in healthy male volunteers		200 mg/m^2	Sequence-randomized single-dose, 3-way crossover of 200 mg/m^2 ganetespib vs 400 mg moxifloxacin PO vs vehicle placebo control
9090-14 *Phase 3*	Randomized, multicenter study in pts with advanced non-small-cell lung adenocarcinoma		Arm A (control): docetaxel 75 mg/m^2 Arm B (experimental): ganetespib 150 mg/m^2 + docetaxel 75 mg/m^2	75 mg/m^2 Day 1, 3 wk cycle Ganetespib Days 1 and 15, each 3-wk cycle Docetaxel Day 1 of each 3-wk cycle
9090-15 *Phase 1*	Drug interaction study examining possible effects of ganetespib on omeprazole PK, a sensitive CYP2C19 substrate, in healthy male volunteers.		200 mg/m^2	Sequence-randomized single-dose 2-way crossover of 20 mg omeprazole with and without 200 mg/m^2 ganetespib

APPENDIX 2. INVESTIGATOR SPONSORED STUDIES

Table 6: Investigator Sponsored Studies

Phase and IST #	Study Description	Dose Levels	Dosing Schedule
Phase 1 9090-110-IST	Study of ganetespib + bortezomib in relapsed/refractory multiple myeloma	Dose Escalation Ganetespib 100-173 mg/m^2 Bortezomib 1.0 mg/m^2 or 1.3 mg/m^2	Ganetespib Days 1, 4, 8, 11 of each 21-day cycle Bortezomib Days 1, 4, 8, 11 of each 21-day cycle
Phase 1 9090-113-IST	Study of ganetespib in rectal cancer	Dose Escalation Ganetespib 60-150 mg/m^2 Capecitabine 825 mg/m^2 BID Radiation 50.4 Gy	Ganetespib 150 mg/m^2 Days -14, -11, -7, -4 followed by dose escalation on Days 1, 8, 15, 29, and 36 Capecitabine plus radiation on Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40
Phase 1 9090-133-IST	Study of ganetespib + ziv-aflibercept in refractory GI, non-squamous NSCLC, urothelial carcinomas and sarcomas	Dose Escalation Ganetespib 100, 150 mg/m^2 Ziv-aflibercept 4 mg/kg	Ganetespib Days 1, 8, 15 of each 28-day cycle Ziv-aflibercept Days 1 and 15 of each 28-day cycle
Phase 1 9090-117-IST	Study of ganetespib with paclitaxel and trastuzumab in HER2+ metastatic breast cancer	Dose Escalation Ganetespib 100-150 mg/m^2 Paclitaxel 80 mg/m^2 Trastuzumab 4 mg/kg on C1D1, 2 mg/kg thereafter	Ganetespib on Days 1, 8, 15 of each 28-day cycle Paclitaxel + trastuzumab Days 1, 8, 15, 22 of each 28-day cycle
Phase 1/2 9090-120-IST	Study of ganetespib with sirolimus in unresectable or metastatic MPNST	Dose Escalation Ganetespib 150, 200 mg/m^2 Sirolimus 12 mg loading dose, 4 mg thereafter	Ganetespib Days 1, 8, 15 of each 28-day cycle Sirolimus daily

Phase and IST #	**Study Description**	**Dose Levels**	**Dosing Schedule**
Phase 1/2 9090-122-IST	Study of ganetespib with paclitaxel in recurrent/persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	Dose Escalation Ganetespib 100-150 mg/m^2 Paclitaxel 80 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle Paclitaxel; Days 1, 8, 15 of each 28-day cycle
Phase 1/2 9090-125-IST	Study of ganetespib with paclitaxel in metastatic, p53-mutant, platinum-resistant ovarian cancer	Dose Escalation Ganetespib 100-150 mg/m^2 Paclitaxel 80 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle Paclitaxel Days 1, 8, 15 of each 28-day cycle
Phase 1/2 9090-114-IST	Study of Ganetespib + Crizotinib in ALK rearranged NSCLC	Dose Escalation Ganetespib 100-200 mg/m^2 Crizotinib 250 mg BID	Ganetespib Days 1 and 8 of each 21-day cycle Crizotinib daily
Phase 1/2 9090-115-IST	Study of Ganetespib with Pemetrexed-Platinum, in Patients With Malignant Pleural Mesothelioma (MESO-02)	Dose Escalation Ganetespib 100-200 mg/m^2 Pemetrexed 500 mg/m^2 Cisplatin 75 mg/m^2 or Carboplatin AUC5	Ganetespib Days 1 and 15 of each 21-day cycle Pemetrexed Day 1 of each 21-day cycle Cisplatin or Carboplatin on Day 1 of each 21-day cycle
Phase 2 9090-135-IST	Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2 (I-SPY-2)	Ganetespib 150 mg/m^2 Paclitaxel 80 mg/m^2	Ganetespib Days 1, 8, 15 of 28-day cycle during Cycles 1-3, 5-7, 9-11 Paclitaxel weekly cycles 1-12

Phase and IST #	**Study Description**	**Dose Levels**	**Dosing Schedule**
Phase 2 9090-136-IST	Translational Study of ganetespib and docetaxel in advanced adenocarcinoma NSCLC	Ganetespib 150 mg/m^2 Docetaxel 75 mg/m^2 Pretreatment tumor biopsy obtained w/in 3 days prior to initial dosing (Day -7 for Cohort 1, Day 21 for Cohort 2). Post treatment tumor biopsy obtained w/in 24 hours of initial dosing.	Ganetespib Days1 and 15 of each 21-day cycle Docetaxel Day 1 of each 21-day cycle
Phase 2 9090-106-IST	Study of ganetespib, in metastatic ocular melanoma	Ganetespib 150 mg/m^2	Ganetespib Days 1, 4, 8, 11, 15, 18 of each 28-day cycle
Phase 2 9090-116-IST	Study of ganetespib + fulvestrant in HRT receptor + MBC	Ganetespib 200 mg/m^2 Fulvestrant 500 mg	Ganetespib Days 1, 8, 15 of each 28-day cycle Fulvestrant Days 1 and 15 of Cycle 1 and Day 1 only of each subsequent 28-day cycle
Phase 2/3 9090-112-IST	Study of ganetespib + LD Ara-C in elderly AML pts	Ganetespib 120 mg/m^2 Ara-C 20 mg BID	Ganetespib Days 1, 8, 15, 22, 29 of 42-day cycle Ara-C Days 1-10 of 42-day cycle
Phase 3 9090-123-IST	Study of Ganetespib + Chemotherapy in Older AML and MDS Pts	Ganetespib 100 mg/m^2 Chemotherapy SOC dose	Ganetespib Days 1, 8, 15 of 28-day cycle during Cycles 2-4 Chemotherapy Days 1, 8, 15 of 28-day cycle during Cycles 1-3
Phase 1 9090-103-IST	Study of ganetespib in advanced hepatocellular carcinoma	Dose Escalation 100-200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle

Phase and IST #	**Study Description**	**Dose Levels**	**Dosing Schedule**
Phase 1B/2 9090-119-IST	Study of ganetespib + chemotherapy in older AML and MDS pts	Ganetespib 100 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-101-IST	Study of ganetespib in advanced esophagogastric cancers	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-104-IST	Study of ganetespib in refractory metastatic colorectal cancer	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-102-IST	Study of ganetespib, in relapsed or refractory small cell lung cancer	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-105-IST	Study of ganetespib in metastatic pancreatic cancer	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-107-IST	Study of ganetespib in metastatic castration-resistant prostate cancer	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-108-IST	Study of ganetespib in metastatic breast cancer	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle
Phase 2 9090-111-IST	Study of ganetespib in unresectable Stage III or Stage IV melanoma	Ganetespib 200 mg/m^2	Ganetespib Days 1, 8, 15 of each 28-day cycle